AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,997	02/19/2004	Anandi Krishnan	12895/46001	5325

26646 7590 01/31/2006

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,997	KRISHNAN ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *15,17 and 20-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 16 and 18-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment submitted on November 14, 2005. Claims 1-48 are pending in the application with claims 15, 17 and 20-48 being withdrawn as drawn to a non-elected invention. Accordingly, claims 1-14, 16 and 18-19 are being examined on the merits herein.

The objection to claim 16 is withdrawn in view of Applicant's amendment to the claim to correct the typo-type error.

The rejection of claim 14 under 35 U.S.C. 112, second paragraph, as being indefinite for lacking antecedent basis for the term "third disintegrant" is withdrawn in view of Applicant's amendment to change the dependency of claim 14 from claim 11 to claim 13, which claim does have proper antecedent basis for the term.

Applicant's arguments filed November 14, 2005 with regards to the rejection of the claims under 35 U.S.C. 103(a) have been fully considered but they are not persuasive. Accordingly, the rejection of record under 35 U.S.C. 103(a) is being maintained. The rejection is repeated below for Applicant's benefit.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14, 16 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,346,533 to Cha et al, issued February 12, 2002, in view of U.S. Patent No. 5,707,975 to Francois et al, issued January 13, 1998, U.S. Patent No. 6,509,038 to Baert et al, issued January 21, 2003, and U.S. Patent Application Publication No. 2003/0104066 to Murai et al, published June 5, 2003.

Cha et al. teaches a pharmaceutical composition for oral administration of itraconazole that exhibits improved solubility and bioavailability (see column 1, lines 10-67, in particular.) Cha et al. teaches that solubility of the drug is improved by dissolving the itraconazole in an organic solvent and dissolution drying the mixture to form particles (see column 2, lines 1-10, in particular.) Cha et al. exemplifies a method of dissolution drying spray drying as well as via a fluid bed granulator (see Examples 2-3, column 3, line 54 through column 4, lines 10, in particular), which is the same granulation method exemplified in Examples 1-3 of Applicant's specification. Cha et al. teaches that pharmaceutical excipients can also be provided in the dissolution-induced

drying step, including a binder, a disintegrant, a stabilizer, or another active material (see column 2, line 63 through column 3, lines 2, in particular.) Cha et al. furthermore exemplifies compositions that are uniformly mixed (see column 4, lines 25-35, in particular), and thus is considered to teach granules having itraconazole distributed uniformly throughout.

Regarding claim 2, Cha et al. teaches that the composition can be provided in the form of a tablet or capsule (see column 3, lines 34-48, in particular.) Regarding claim 3, Cha et al. teaches providing itraconazole.

Cha et al. does not specifically teach granules that are non-spherical. Cha et al. also does not specifically teach part (b) of claims 1 and 16, namely providing a bulking agent that is microcrystalline cellulose. Cha et al. furthermore does not specifically teach granules having a disintegrant that is croscarmellose sodium (part (c)), a binding agent that is polyvinyl pyrrolidone (part (d)) or an acid that is hydrochloric acid (part (e)), as recited in claims 1 and 16.

Regarding part (e) of claim 1 and also claim 8, namely the limitation that the acid is hydrochloric acid, the teachings of Francois et al. are noted. Francois et al. teaches a formulation for oral administration of an antifungal agent (see abstract, in particular.) Francois et al. teaches that antifungal agents such as itraconazole have improved solubility and dissolution rate in organic solvents comprising alcoholic co-solvents, such

as ethanol, combined with an acidic medium, such as a hydrochloric acid solution (see column 1, lines 5-50 and column 3, lines 40-67, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention as made would have found it obvious to substitute the hydrochloric acid-containing solvent of Francois et al. into the granule preparation method of Cha et al, and thereby forming granules having hydrochloric acid, because Cha et al. teaches the itraconazole is dissolved in an organic solvent prior to dissolution drying, and Francois et al. teaches an organic solvent comprising hydrochloric acid that exhibits a good dissolution of itraconazole. Thus, one of ordinary skill in the art would have been motivated to provide the hydrochloric-acid containing solvent medium of Francois et al. in the method of Cha et al, thereby forming granules containing hydrochloric acid, with the expectation of providing a solvent medium suitable for dissolving the itraconazole drug prior to the dissolution drying step.

Regarding parts (b) and (c) of claim 1 and also claims 4-5, it is noted that Baert et al. teaches antifungal compositions with improved bioavailability having particles comprising itraconazole (see abstract, in particular.) Baert et al. teaches that suitable disintegrants that can be provided with the itraconazole particles can include crosslinked sodium carboxymethylcellulose (croscarmellose sodium.) (See column 8, lines 31-45, in particular.) Baert et al. further teaches that the composition can comprise a diluent or filler (bulking agent) to provide the desired disintegration rate and

bioavailability of the itraconazole, and that suitable diluents or fillers can comprise microcrystalline cellulose.)

Regarding part (d) of claim 1 and also claim 7, it is noted that Murai et al. teaches easy-to-take granules comprising an active ingredient, such as itraconazole (see abstract and paragraph 39, in particular.) Murai et al. teaches that a binder suitable for such a granulated composition can include polyvinyl pyrrolidone (see paragraph 42, in particular.)

Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the microcrystalline cellulose bulking agent and croscarmellose sodium disintegrant of Baert et al. and the polyvinylpyrrolidone binder of Murai et al. in the composition formed by Cha et al. and Francois et al, because Cha et al. and Francois et al. teach forming granules which can include a binder a disintegrant or another active material, and Baert et al, and Murai et al. teach disintegrants, active materials comprising fillers or diluents, and binders that are suitable for oral compositions comprising particles. Accordingly, one of ordinary skill in the art would have been motivated to provide the disintegrant, filler and binder of Baert et al. and Murai et al. in the granule composition of Cha et al. and Francois et al. with the expectation of providing suitable pharmaceutical excipients in the granule composition.

Regarding the limitation that the composition comprises non-spherical granules as in claim 1, it is noted that Applicant's guidance in the specification as to the means of formation of the claimed non-spherical granules is limited to a description of the composition used to form the granules, and a statement that the granules are generated from the composition via a fluid bed granulator (as in Examples 1-3 of Applicant's specification, for example.) As discussed above, the teachings of Cha et al, Francois et al, Baert et al. and Murai et al. render the granule composition obvious, and Cha et al. also exemplifies fluid bed granulation as a method of forming the granules (see Example 2, in particular.) Accordingly, it is considered that the claimed non-spherical granules are also rendered obvious by the teachings of Cha et al, Francois et al, Baert et al, and Murai et al, as the granule-forming method taught by the combined references is the same as that taught in the specification as being capable of generating non-spherical granules.

Accordingly, the combined teachings of Cha et al, Francois et al, Baert et al. and Murai et al. render obvious the pharmaceutical compositions of claims 1-5, 7-9 and 16.

Regarding the disintegrant comprising the mixture of croscarmellose sodium and crospovidone that is recited in claim 6, or the limitation that the granules comprise a second disintegrant as in claims 11-12, it is noted that Baert et al. teaches that suitable disintegrants include croscarmellose sodium as well as crosspovidone (see column 8, lines 31-40, in particular.) Note it is considered that "[I]t is prima facie obvious to

combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.) Accordingly, it would have been obvious to provide a combination of the disintegrants taught as being suitable by Baert et al. in the composition of Cha et al, Francois et al, and Murai et al, with the expectation of providing suitable disintegrants for the composition.

Regarding claims the limitation of claims 13-14 that the granules comprise a third disintegrant selected from the group consisting of crospovidone, croscarmellose sodium and sodium starch glycolate, in addition to a second disintegrant, it is noted that Murai et al. also teaches that suitable disintegrators for particle compositions (see paragraph 0036, in particular.) Murai et al. provides examples of multiple disintegrators, including hydroxypropyl starch and corn starch (see paragraph 0036, in particular.) Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to combine one of the disintegrators taught by Murai et al, for example as a

second disintegrant, with a first disintegrant comprising croscarmellose sodium and a third disintegrant comprising crospovidone, as taught by Baert et al, and provide the disintegrators in the composition taught by the combination of Cha et al, Francois et al, Baert et al, and Murai et al, with the expectation of providing suitable disintegrants in the composition.

Regarding the limitation recited in claims 9-10 that the granules comprise a cyclodextrin, Francois et al. teaches that the solubility and bioavailability of compounds such as itraconazole is increased by complexation with cyclodextrins (see column 1, lines 14-26, in particular.) Francois et al. teaches that such solubilizing cyclodextrins include β-cyclodextrin derivatives such as 2-hydroxypropyl-β-cyclodextrin (see column 2, lines 15-20, in particular.) Francois et al. furthermore teaches that cyclodextrins can be provided with the organic solvent comprising the acid and alcoholic co-solvent to improve solubility of itraconazole (see column 3, lines 40-56, in particular.) Accordingly, one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the cyclodextrins of Francois et al. in the composition taught by Cha et al, Baert et al. and Murai et al, with the expectation of improving the solubility and bioavailability of itraconazole in the composition.

Claim 18 differs from the limitations recited in claim 1 in that the claim recites the granules having a croscarmellose sodium and crospovidone mixture, and also recites the granules comprising cyclodextrin. Claim 19 includes the further limitation that the

cyclodextrin in hydroxypropyl- β-cyclodextrin. However, as discussed above, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide these components as a part of the granule composition of Cha et al, Francois et al, Baert et al, and Murai et al, because Baert et al. teaches that suitable disintegrants for the composition can include croscarmellose sodium and crospovidone, and Francois et al. teaches that cyclodextrins such as hydroxypropyl- β-cyclodextrin improve the solubility and bioavailability of itraconazole. Accordingly, the composition recited in claims 18-19 is rendered obvious by the combined teachings of Cha et al, Francois et al, Baert et al. and Murai et al.

Response to Arguments

Applicant's arguments filed November 14, 2005, have been fully considered but they are not persuasive.

Applicant argues that it is not obvious to combine the teachings of Francois et al. with those of Cha et al. In particular, Applicant argues that Francois teaches that acid should not be used in a granular formulation. However, the Examiner disputes this statement, and instead notes that Francois et al. does not comment on the suitability of acid in granular formulations, such as that of Cha et al, and instead the teachings of Francois et al. are directed to a liquid itraconazole formulation (see column 1, lines 40-50, in particular.)

Applicant's further note that Francois et al. teaches that prior art formulations such as strong acidic formulations and other acidic formulations exhibited some problems with regards to ease-of-preparation, acceptability and palatability (see column 1, lines 20-30, in particular.) Nonetheless, Francois et al. teaches that the inventive composition comprises an aqueous acidic medium as the bulk liquid carrier (see column 1, lines 40-50, in particular), and even teaches an acidic pH range of such a carrier, such as a hydrochloric-acid containing carrier, that provides optimum bioavailability and is sufficiently stable (see column 3, lines 58-68, in particular.) Accordingly, the teachings of Francois et al. as a whole cannot be reasonably understood to constitute a teaching away from the use of acid such as hydrochloric acid in oral antifungal formulations of itraconazole, as asserted by Applicant.

Furthermore, it is noted that the Francois et al. reference is relied on for the reference's teachings of the improved solubility and dissolution rate itraconazole in organic solvents comprising alcoholic cosolvents, such as ethanol, and combined with an acidic medium such as a hydrocholic acid-containing medium (see column 3, lines 40-66, in particular.) Francois clearly teaches that itraconazole is only sparingly soluble in water, and that acidic formulations improve the dissolution of itraconazole (see column 1, lines 15-40, in particular.) As Cha et al. teaches the itraconazole is dissolved in an organic solvent prior to dissolution drying, it is considered that it would have been obvious to select the solvent of Francois et al, which exhibits improved itraconazole

solubility, in the method of Cha et al, with the expectation of providing an organic solvent capable of providing adequate solubilizing of the itraconazole prior to the dissolution drying step, and thereby resulting in an antifungal composition having the remaining acid after drying of the antifungal composition. Accordingly, the teachings of Francois et al. are being relied on for the teaching of a suitable solvent for the method of Cha et al, which necessarily results in a composition having the acid, as recited in the claims.

Applicant furthermore argues that Cha et al. teaches granular preparations of itraconazole, and thus teaches a dry formulation and not an organic solvent. The Examiner notes that Cha et al. nonetheless teaches dissolving the itraconazole in an organic solvent prior to drying (see column 2, lines 1-10, in particular), and thus teaches the use of such a solvent in the preparation method. Accordingly, one of ordinary skill in the art would be motivated to provide an organic solvent capable of dissolving itraconazole, such as that taught by Francois et al., in the granular preparation method and composition of Cha et al.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Regarding Applicant's argument that the references do not specifically teach non-spherical granules, it is noted that the teachings of Cha et al, Francois et al, Baert et al. and Murai et al. render the granule composition obvious, and Cha et al. also exemplifies fluid bed granulation as a method of forming the granules (see Example 2, in particular.) It is furthermore noted that one of ordinary skill in the art would have found it obvious to vary and/or optimize parameters in the fluid bed granulation method of Cha et al, according to the guidance provided by Cha et al, to arrive at a composition having desired properties for the oral administration of itraconazole, such as parameters that yield non-spherical granules. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Accordingly, since the combined teachings of the reference renders the claimed composition obvious, the property of such a claimed composition will also be rendered obvious by the prior art teachings, since the properties, namely the non-spherical nature of the product, are inseparable from its composition. Therefore, if the prior art teaches the composition or renders the composition obvious, then the properties are also taught

or rendered obvious by the prior art. In re Spada, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990.) See MPEP 2112.01. The burden is shifted to Applicant to show that the prior art product does not possess or render obvious the same properties as the instantly claimed product.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AMC

SHENGJUN WANG
PRIMARY EXAMINER